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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,440	03/12/2004	Tai Chih Kuo	KUOT3010/EM	5252
23364	7590	04/20/2005	EXAMINER	
BACON & THOMAS, PLLC 625 SLATERS LANE FOURTH FLOOR ALEXANDRIA, VA 22314			DESAI, ANAND U	
			ART UNIT	PAPER NUMBER
			1653	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/798,440

Applicant(s)

KUO ET AL

Examiner

Anand U. Desai, Ph.D.

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 January 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to Amendment filed on January 14, 2005. Claims 1-22 are currently pending and are under examination.

Maintenance of Objections and Rejections

Specification

2. The abstract of the disclosure is objected to because there is a typographical error. There are two period punctuation marks on line 7 of the abstract. Correction is required. See MPEP § 608.01(b).
3. Applicants amendment submitted on January 14, 2005 states on page 2 that an amended Abstract has been submitted on a separate sheet. The amended Abstract is not seen in the application file?
4. The amendment to page 8, line 29 of the specification is not clearly identified. The verb “was” has been changed to “were” without the proper underline marking to show the change.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
6. Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
7. What defines a “substrate” in claims 1, and 22? What is being fabricated in claim 1?
8. In claim 1, it is unclear how one is tagging a DNA sequence? Please clarify.

Art Unit: 1653

9. In claims 14, and 21, GST is not defined. Suggest amending claim 2 to include an abbreviation for “glutathione S transferase (GST)” or identifying GST as glutathione S transferase in claims 14 and 21.

10. Claims 2-13, 15-20 are rejected for depending on a rejected claim.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. Applicant’s amendment asserts on page 9, 4th paragraph of the Remarks that no New Matter has been added and states that all of the amendments are fully supported by the original disclosure of the application, for support of the newly added limitation “fabricating a substrate” in claim 1. However, the specification does not appear to provide an adequate written description of a method for “fabricating a substrate”. The specification discloses the general method of purifying, modifying, and immobilizing recombinant proteins. The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce

Art Unit: 1653

new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the New Matter in the response to this Office Action. Alternatively,

Applicant is invited to clearly point out the written support for the instant limitations.

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." The introduction of claim changes, which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

Art Unit: 1653

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Enomoto, S. et al. (Biotechnology 24: 782-788 (1998)) in view of Cosma, A. (U.S. Patent 6,150,123), and Terpe, K. (Appl. Microbiol. Biotechnol. 60: 523-533 (2003)).

Enomoto, S. et al. disclose the construction of a series of vectors for the expression of epitope- and affinity-tagged fusion proteins in yeast and *E. coli*. The affinity tag is composed of six consecutive histidine residues that enables the facile purification of a fusion protein on metal columns (see p.782, Introduction). Enomoto, S. et al. transformed both yeast and *E. coli* with a vector containing a gene for RLF2, which encodes for the large subunit of yeast chromatin assembly factor I (see p. 784, section on Functional Complementation from YGALSET Vector). The RLF2p fusion proteins expressed in *E. coli* or *S. cerevisiae* have been specifically enriched on commercially available nickel columns (Ni-NTATM, QIAGEN) (see p. 786, First paragraph upper left hand corner). Enomoto, S. et al. do not disclose the step of immobilizing the fusion protein.

Cosma, A. discloses a method for detectably labeling with biotin a subset of a larger population of proteins comprising first (i) contacting the larger population of proteins with an affinity element, attached to a solid phase element, which selectively binds to the subset of proteins, under conditions which permit binding of the affinity element to the subset of proteins to occur; (ii) removing protein not bound to the solid phase element; and (iii) linking biotin to the subset of proteins bound to the solid phase element ("biotinylation") (see column 2, lines 44-53). Cosma, A. also discloses elution of the biotinylated protein from an affinity column by ligand or

Art Unit: 1653

a competitive inhibitor of the ligand-ligand partner interaction, or maybe eluted by altering conditions such as ionic strength or pH of an elution buffer (see column 3, lines 55-60).

Terpe, K. discloses the importance of immobilization of biologically active proteins for research and industry (see Conclusion section, last three sentences). Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to express a tagged protein according to the process of Enomoto, S. et al., and recover the recombinant protein using a metal chelation column that binds the histidine tag. Although Enomoto, S. et al. does not provide the last step of immobilizing a recombinant protein on a substrate as currently claimed, Terpe, K. provides the state of knowledge in the art and the motivation to immobilize proteins to study functional domains of biologically active proteins once they are immobilized. Further, Cosma, A. discloses the process of accomplishing this by labeling a tagged protein with biotin. It is well known in the art that biotin binds avidin. Therefore, it would have been obvious to the person having ordinary skill in the art to expect to succeed in immobilizing a biotinylated protein with an avidin-conjugated substrate, and one would have been motivated to immobilize a biotinylated protein with an avidin-conjugated substrate during the process of studying the functional domain of the immobilized protein, to thereby manufacture a substrate as currently claimed (current application, claims 1-22).

Art Unit: 1653

Response to Remarks

Applicants traverse the rejection of claims 1-22 under 35 U.S.C. 103(a). Applicants cite MPEP 2143, which describes the three basic criteria to establish a prima facie case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In addition, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants have amended claim 1 to describe a method for fabricating a substrate by purification, modification, and immobilization of recombinant protein onto a substrate.

Applicant states the object of the biotinylating step in the present invention is used for protein immobilization but not for purification. Applicant states the major purpose of utilizing the affinity of biotin and avidin in the present invention is for immobilizing a recombinant protein onto a substrate to fabricate an immobilized substrate for the subsequent applications. Applicants further state the specification of the current application may not be used as a teaching reference to combine the teachings and arrive at Applicant's claimed invention. *In re Fritch*, 23 USPQ 1780, 1784 (Fed. Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.").

17. Applicant's arguments have been fully considered but they are not persuasive as the citations applied to describe the state of the art. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Enomoto et al. does teach the recombinant expression of a fusion protein comprising both an epitope- and affinity-tag. Therefore, describing the state of the art for expression of recombinant proteins with multiple domains, each domain conferring a distinct functional effect. Cosma, A. et al. does describe the ability of biotinylating an immobilized protein, where the immobilized domain was distinct from the domain labeled with biotin. Therefore, it would have been obvious to the person having ordinary skill in the art to biotinylate a His-tagged recombinant protein using the molecular biological and chromatographic steps as disclosed by the state of the prior art, as evidenced by Enomoto et al. and Cosma, A. et al. Further, biotin conjugated proteins would be immobilized during an affinity chromatography purification method using avidin-conjugated supports. An avidin-conjugated support could be reasonably

interpreted to be a substrate as being claimed. Terpe, K. et al. provides the motivation in the state of the art to manufacture a substrate comprising an immobilized protein to study functional domains of the biologically active protein. Therefore, one of ordinary skill in the art would have expected to succeed in immobilizing a biotinylated protein with an avidin-conjugated substrate, to thereby manufacture a substrate as currently claimed.

Art of Record

18. Wilchek, M. et al. (Methods in Enzymology, 184: 5-13 (1990)). Wilchek, M. et al. disclose an overview of avidin-biotin technology. Wilchek, M. et al. disclose the immobilization of a biotin-conjugated molecule with an avidin-conjugated solid support (see page 7, Figure 1, Probes box, last item-solid supports, and also page 12, Table II, middle of table, Immobilized avidin).

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

Art Unit: 1653

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

April 13, 2005

